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REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the following remarks.

As an initial matter, applicants appreciate the courtesy extended by the Examiner during the informal telephone interview conducted on July , 2004, during which the content of the advisory action was discussed.

Claim 1, 2, and 12-13 have been amended to correct minor typographical errors. Claim 2 has been amended to more particularly point out that the kit comprises a solution comprising two components, e.g., (a) [^{125}I][N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^{4}]-MCH(4-19) and (b) a buffer . No new matter has been introduced into the application by the instant amendments. Support for the amendments may be found throughout the specification as filed and in the originally presented claims. More particularly, support for the amendment to claim 2 can be found, for example at page 52, penultimate line to page 53, line 3.

Claims 2 and 14 were rejected under 35 U.S.C. §112, second paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Claim 2 as amended, particularly points out and distinctly claims kits comprising a solution comprising (a) [^{125}I][N-(3-(4- hydroxy -3-iodophenyl)propionyl)-Met^{4}]-MCH(4-19) and (b) a buffer. Thus, the claims, as amended, are fully compliant with the requirements of 35 U.S.C. §112, including the requirements of §112, second paragraph.

Applicants respectfully request withdrawal of the rejection and reconsideration of the claims.

Claims 1,2, and 12-14 were rejected under 35 U.S.C. §103(a) as being allegedly anticipated by Ames (U.S. Patent Publication 2002/0038007) in view of Maratos-Flier (U.S. Patent 5,849,708) and Bolton et al. (*Biochem. J.*, 1973, 133:529-539).

The rejection is traversed.

In the remarks section of the Advisory action, the Examiner has indicated that the Declaration under Rule 1.132 filed on April 28, 2004 was insufficient because certain control experiments were not conducted. More particularly, the Examiner averred that the unexpected results obtained by the claimed invention could not be assessed because the data presented in the Declaration did not include antagonist activity for underivatized MCH fragments.

The attached supplemental Declaration under Rule 1.132 provides the additional data requested by the Examiner in the Advisory Action in order to establish the unexpected results for BH-MC(4-19).

Claim 1, as amended, provides screening assays for new compounds capable of binding to SLC-1 which assays utilize MCH derivatives, particularly a ^{125}I labeled derivative of MCH(4-19), e.g., [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19) which was prepared using the Bolton-Hunter (BH) reagent.

In contrast, Ames recites variants of SLC-1 prepared by splicing. Ames neither discloses nor suggests MCH derivatives and more particularly does not disclose or suggest iodo derivatives of MCH (such as radiotopically labeled iodo derivatives). Moreover Ames neither discloses nor suggests the use of iodized MCH derivatives such as [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19) in methods of screening for compounds capable of binding to SLC-1.

No combination of Ames, Maratos-Flier and/or Bolton teach or suggest the use of iodinated MCH derivative, particularly radiolabelled [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19) in assays to screen for other compounds capable of binding to SLC-1. Moreover, no combination of the cite documents provide any motivation to prepare [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19) for any purpose or to prepare a kit comprising a buffer and [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19).

It is generally known to those of ordinary skill in the art that the physiological activity of MCH is destroyed by iodinization such that MCH derivatized with the BH reagent is not suitable for use in binding assays. For example, when MCH was derivatized using the BH reagent, the activity of the derivatized MCH was reduced by 3.5 fold compared to underivatized MCH. Similarly, derivatized MCH fragments{BH-MCH(2-19), BH-MCH(3-19), and BH-MCH(5-19)} each possesses reduced agonist activity compared to MCH. Consequently, tritiated MCH derivatives have been prepared and used in binding assays (See, *J. Receptor Signal Transduct. Res.*, Vol 15, pp. 487-502 (1995)).

The specification provides data showing that various iodized MCH derivatives, prepared using the BH reagent, have reduced binding affinity for SLC-1 when compared to MCH. Data was obtained using the GTPγS binding assay. See Example 22 and Figure 8 of the instant specification and the Declaration under Rule 1.132 executed by Dr. Mori on July 28, 2004 attached herewith as Appendix A.

Applicants have surprisingly discovered that iodized MCH(4-19) possesses increased agonist activity than MCH itself, underivitized MCH fragments, and other BH-derivitized fragments. That is, [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19) possesses a greater binding affinity for SLC-1 than MCH, MCH(2-19), MCH(3-19), MCH(4-19), MCH(5-19), MCH(6-19), MCH(7-19), BH-MCH(2-19), BH-MCH(3-19), and BH-MCH(5-19) based on EC_{50} values. This result is shown in 21 and 22 and in Figures 78 and 8 of the present

invention and the Declaration under Rule 1.132 executed by Dr. Mori on July 28, 2004, attached herewith as Appendix A.

Thus, the superior affinity data for BH-MCH(4-19) compared to underivatized MCH, MCH fragments, derivatized MCH and other derivatized MCH fragments would not have been expected to one of ordinary skill in the art based on any combination of the documents relied upon in formulating the outstanding §103 rejections.

Claims 1, 2, and 12-14 were rejected under 35 U.S.C. §103(a) as being allegedly anticipated by Salon (U.S. Patent 6,221,616) in view of Maratos-Flier (U.S. Patent 5,849,708) and Bolton et al. (*Biochem. J.*, 1973, 133:529-539).

The rejection is traversed.

Claim 1, as amended, provides screening assays for new compounds capable of binding to SLC-1 which assays utilize MCH derivatives, particularly a ^{125}I labeled derivative of MCH(4-19), e.g., [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19) which was prepared using the Bolton-Hunter (BH) reagent.

In contrast, Salon recites an MCH receptor, which has an amino acid sequence with 99.8% homology to that of SLC-1. However, Salon neither discloses nor suggests any MCH derivatives and more particularly does not disclose or suggest iodinated MCH derivatives such as [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19). Salon neither discloses nor suggests MCH derivatives and more particularly does not disclose or suggest iodo derivatives of MCH (such as [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19)) or screening assays using same.

No combination of Salon, Maratos-Flier and/or Bolton teach or suggest the use of iodinated MCH derivative, particularly radiolabelled [^{125}I]-{N-(3-(4-hydroxy-3-

iodophenyl)propionyl)-Met^4}-MCH(4-19) in assays to screen for other compounds capable of binding to SLC-1. Moreover, no combination of the cite documents provide any motivation to prepare [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19) for any purpose or to prepare a kit comprising a buffer and [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19).

It is generally known to those of ordinary skill in the art that the physiological activity of MCH is destroyed by iodinization such that MCH derivatized with the BH reagent is not suitable for use in binding assays. For example, when MCH was derivatized using the BH reagent, the activity of the derivatized MCH was reduced by 3.5 fold compared to underivatized MCH. Similarly, derivatized MCH fragments {BH-MCH(2-19), BH-MCH(3-19), and BH-MCH(5-19)} each possess reduced agonist activity compared to MCH. Consequently, tritiated MCH derivatives have been prepared and used in binding assays (See, *J. Receptor Signal Transduct. Res.*, Vol 15, pp. 487-502 (1995)).

The specification provides data showing that various derivatized MCH fragments, prepared using the BH reagent, have reduced binding affinity for SLC-1 when compared to MCH. Data was obtained using the GTPγS binding assay. See Example 22 and Figure 8 of the instant specification and the Declaration under Rule 1.132 executed by Dr. Mori attached herewith as Appendix A.

Applicants have surprisingly discovered that BH-MCH(4-19) possesses increased agonist activity than MCH itself. That is, [^{125}I]-{N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4}-MCH(4-19) possesses a greater binding affinity for SLC-1 than MCH (or any one of MCH(2-19), MCH(3-19), MCH(4-19), MCH(5-19), MCH(6-19), MCH(7-19), BH-MCH(2-19), BH-MCH(3-19), and BH-MCH(5-19)). This result is shown in Examples 21 and 22 and Figures 7 and 8 of the present invention and the Declaration under Rule 1.132 executed by Dr. Mori attached herewith as Appendix A. Applicants have further discovered that BH-MCH(4-19) exhibits high SLC-1 binding specificity (see Example 23 and Figure 9 of the present invention).

Thus, the superior affinity data for BH-MCH(4-19) compared to other MCH derivatives and MCH itself would not have been expected to one of ordinary skill in the art based on any combination of the documents relied upon in formulating the outstanding §103 rejections.

Claims 1, 2, and 12 are patentable over any combination of Salon, Maratos-Flier, and Bolton. Claim 13 and 14 depend from claim 1 or 14 and are therefore also patentable over any combination of the cited documents Salon, Maratos-Flier, and Bolton.

Applicants request reconsideration of the claims and allowance of the application.

Although it is not believed that any additional fees are needed to consider this submission, the Examiner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Early consideration and allowance of the application are earnestly solicited.

Respectfully submitted,

August 3, 2004

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APPENDIX A

DECLARATION UNDER 37 C.F.R. 1.132 BY DR. MASAAKI MORI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Masaaki MORI et al. Docket No. 506001 (46342)

Serial No. 09/869,540 Examiner: Jiang, Doug

Filed: June 27,2001 Group Art Unit: 1646

For: SCREENING METHOD

DECLARATION UNDER 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Masaaki MORI, the undersigned, a citizen of Japan residing at 3-8-5, Kasuga, Tsukuba-shi, Ibaraki 305-0821, JAPAN do hereby declare:

That I am an employee of the Assignee of the above-identified application;

That I graduated from University of Tokyo with the degree of Bachelor of Agriculture in March, 1978, and received a Ph. D. from University of Tokyo for a thesis entitled "Chemical studies on the sex pheromones in Streptococcus faecalis" in March, 1985;

That I was a postdoctoral fellow at University of Tokyo as a recipient of Japan Society for the Promotion of Science research fellowships for young scientists from April, 1985 to March, 1987;

That I have been employed by Takeda Chemical Industries, Ltd., Osaka, Japan, since April, 1987, and have been engaged in pharmaceutical research of said company,

That I was a visiting scientist in U.S.-Japan Biomedical Research Laboratories, Tulane University School of Medicine from May, 1988 to July, 1989;

That I am a member of the Japan Society for Bioscience, Biothechnology, and Agrochemistry, the Japanese Biochemical Society, the Japanese Peptide Society, and the Japanese Pharmacological Society, and published with other research workers, a number of reports on scientific studies, among others, including

(1) Purification of acidic fibroblast growth factor from bovine omentum, Biochem. Biophys. Res. Commun., 161, 169-175 (1989), Tetsuya Ohtaki, Kaori Wakamatsu, Masaaki Mori, Yoshihiro Ishibashi, Tadashi Yasuhara;

(2) Oxytocin is the major prolactin releasing factor in the posterior pituitary, Endocrinology, 126, 1009-1013 (1990), Masaaki Mori, Sandor Vigh, Atsuro Miyata, Tadashi Yoshihara, Shusaku Oka, Akira Arimura;

(3) Isolation and identification of hemin as an endogenous Na^+/K^+-ATPase inhibitor from porcine blood cells, Biochem. Biophys. Res. Commun., 178, 95-103 (1991), Tadashi Yasuhara, Masaaki Mori, Kaori Wakamatsu, Kazuki Kubo;

(4) Isolation and identification of melanin-concentrating hormone as the endogenous ligand of the SLC-1 receptor, Biochem. Biophys. Res. Commun., 261, 622-626 (1999), Yukio Shimomura, Masaaki Mori, Tsukasa Sugo, Yoshihiro Ishibashi, Michiko Abe, Tsutomu Kurokawa, Haruo Onda, Osamu Nishimura, Yasuhiro Sumino, Masahiko Fujino;

(5) Urotensin II is the endogenous ligand of a G-protein-coupled orphan receptor, SENR (GPR14), Biochem. Biophys. Res. Commun., 265, 123-129 (1999), Masaaki Mori, Tsukasa Sugo, Michiko Abe, Yukio Shimomura, Mika Kurihara, Chieko Kitada, Kuniko Kikuchi, Yasushi Shintani, Tsutomu Kurokawa, Haruo Onda, Osamu Nishimura, Masahiko Fujino;

(6) Cloning of a novel G protein-coupled receptor, SLT, a subtype of the melanin-concentrating hormone receptor, Biochem. Biophys. Res. Commun., 283, 1013-1018 (2001), Masaaki Mori, Mioko Harada, Yasuko Terao, Tsukasa Sugo, Takuya Watanabe, Yukio Shimomura, Michiko Abe, Yasushi Shintani, Haruo Onda, Osamu Nishimura, Masahiko Fujino;

(7) T-226296: a novel, orally active and selective melanin-concentrating hormone receptor antagonist, Eur. J. Pharmacol., 438, 129-135 (2002), Shiro Takekawa, Asano Asami, Yuji Ishihara, Jun Terauchi, Kaneyoshi Kato, Yukio Shimomura, Masaaki Mori, Hitomi Murakoshi, Koki Kato, Nobuhiro Suzuki, Osamu Nishimura, Masahiko Fujino;

(8) Identification of a neuropeptide modified with bromine as an endogenous ligand for GPR7, J. Biol. Chem., 277, 34010-34016 (2002), Ryo Fujii, Hiromi Yoshida, Shoji Fukusumi, Yugo Habata, Masaki Hosoya, Yuji Kawamata, Takahiko Yano, Shuji Hinuma, Chieko Kitada, Taiji Asami, Masaaki Mori, Yukio Fujisawa, Masahiko Fujino;

(9) Identification of neuropeptide W as the endogenous ligand for orphan G-protein-coupled receptors, GPR7 and GPR8, J. Biol. Chem., 277, 35826-35832 (2002), Yukio Shimomura, Mioko Harada, Mika Goto, Tsukasa Sugo, Yoshio Matsumoto, Michiko Abe, Takuya Watanabe, Taiji Asami, Chieko Kitada, Masaaki Mori, Haruo Onda, Masahiko Fujino;

(10) A role for neuropeptide W in the regulation of feeding behavior, Endocrinology, 144, 4729-4733 (2003), Muhtashan S. Mondal, Hideki Yamaguchi, Yukari Date, Takuya Shimbara, Koji Toshinai, Yukio Shimomura, Masaaki Mori, Masamitsu Nakazato;

(11) Identification of urotensin II-related peptide as the urotensin II-immunoreactive molecule in the rat brain, Biochem. Biophys. Res. Commun., 310, 860-868 (2003), Tsukasa Sugo, Yuko Murakami, Yukio Shimomura, Mioko Harada, Michiko Abe, Yoshihiro Ishibashi, Chieko Kitada, Nobuyuki Miyajima, Nobuhiro Suzuki, Masaaki Mori, Masahiko Fujino; and

(12) Intracerebroventricular administration of urotensin II promotes

anxiogenic-like behaviors in rodents, Neurosci. Lett., 358, 99-102 (2004), Yoshio Matsumoto, Michiko Abe, Takuya Watanabe, Yuka Adachi, Takahiko Yano, Hideki Takahashi, Tsukasa Sugo, Masaaki Mori, Chieko Kitada, Tsutomu Kurokawa, Masahiko Fujino;

That I am one of the inventors of the above-identified patent application (hereinafter referred to as "this application"); and

That I have read the Final Office Action mailed March 9, 2004, including the grounds or remarks provided by the Examiner as to why Claims 1, 2, and 12-14 were considered unpatentable over the cited art.

That this declaration is being submitted to address certain conclusions reached by the Examiner as to the teachings and disclosure of Salon (U.S. Patent 6,221,616) and Ames (U.S. Patent Publication 2002/0038007), each in view of Maratos-Flier (U.S. Patent 849,708) and Bolton (*Biochem. J.*, 1973, 133:529-539), cited in support of the rejection of the claims.

That for at least the reasons set forth below, the method for screening a compound that alters the binding between $[^{125}I][N\text{-}(3\text{-}(4\text{-hydrxoy-}3\text{-iodophenyl})\text{ propionyl})\text{-Met}^4]\text{-MCH(4-19)}$ and SLC-1 provided by the invention is not anticipated or obvious in view of the teachings of Ames in view of Maratos-Flier and Bolton or in view of the teachings of Salon in view of Maratos-Flier and Bolton.

That the following experiments were carried out by myself or under my direction:

EXPERIMENT

Assay for the agonist activity of MCH, MCH(2-19), MCH(3-19), MCH(4-19) and MCH(5-19) derivatized with a non-isotope Bolton-Hunter reagent (hereinafter referred to as "BH reagent"), using the $GTP\gamma S$ binding assay

The agonist activity of the non-isotope BH reagent-derivatized MCH,

MCH(2-19), MCH(3-19), MCH(4-19) and MCH(5-19) obtained in Example 18 was assayed using the GTPγS binding assay as shown in Example 22 of this application.

The derivatized MCH, MCH(2-19), MCH(3-19), MCH(4-19) and MCH(5-19) increased dose-dependently the amount of [^{35}S]-guanosine 5'-(γ-thio)triphosphate bound to the human SLC-1-expression CHO cell membrane fraction, confirming that various MCHs derivatized with a non-isotope Bolton-Hunter reagent exhibit the agonist activity as shown in Fig. 8 of this application.

The results of Example 22 can be represented by EC_{50} values as follows.

	EC_{50} (nM)
MCH	0.55
BH-MCH	1.95
BH-MCH(2-19)	2.64
BH-MCH(3-19)	1.27
BH-MCH(4-19)	0.43
BH-MCH(5-19)	1.95

As shown above, when full-length MCH was derivatized using the BH reagent to prepare BH-MCH, its agonist activity was reduced by 3.5 fold compared to un-derivatized MCH. Surprisingly, it was found that the agonist activity of BH-MCH(4-19) exhibited 4.5 fold activity compared to the BH-MCH, and that its agonist activity is higher than the full-length MCH. Also, it was unexpectedly found that the agonist activity of BH-MCH(4-19) was 6.1 times higher than BH-MCH(2-19); 3.0 times higher than BH-MCH(3-19); and 4.5 times higher than BH-MCH(5-19) although the difference between them resides only in absence or presence of one or two amino acid residues.

In addition, it was confirmed in Example 23 of this application that the [^{125}I]-labeled BH-MCH(4-19) exhibited sufficient SLC-1 binding specificity to extent that the binding inhibition assay can be efficiently carried out (See Example 23 and Fig. 9).

Therefore, to my best knowledge, I believe that the agonist activity of BH-MCH(4-19), i.e., [N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4]-MCH(4-19) was unexpected, and thus use of the radiolabeled BH-MCH(4-19), i.e., [^{125}I]-[N-(3-(4-hydroxy-3-iodophenyl)propionyl)-Met^4]-MCH(4-19) for screening a compound that alters the binding property of MCH and SLC-1 was considered unobvious.

Assay for the agonist activity of MCH, MCH(2-19), MCH(3-19), MCH(4-19), MCH(5-19), MCH(6-19) and MCH(7-19) using the GTPγS binding assay

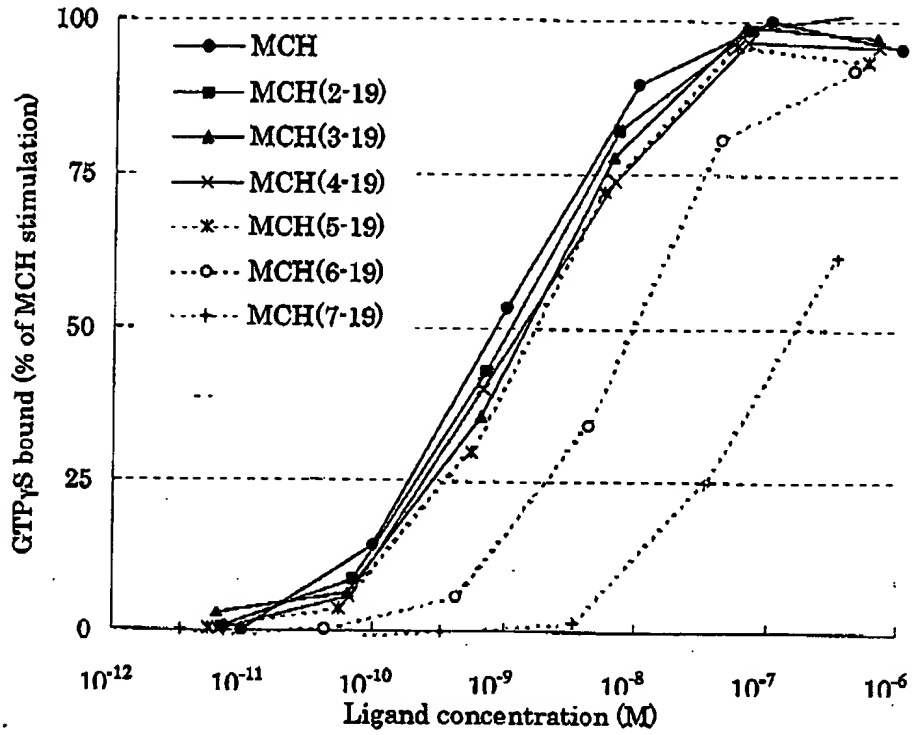
A rat SLC-1-expression CHO cell membrane fraction was prepared by the following procedure. Rat SLC-1-expression CHO cells (1 x 10^8 cells) were suspended in phosphate buffered saline (pH 7.4) supplemented with 5 mM EDTA (ethylenediaminetetraacetic acid) followed by centrifugation. After 10 ml of a homogenate buffer (10 mM $NaHCO_3$, 5 mM EDTA, pH 7.5) was added to the cell pellets, the mixture was homogenized with a polytron homogenizer. The homogenate was then centrifuged at 400 x g for 15 minutes. The resulting supernatant was further centrifuged at 100,000 x g for an hour to give membrane fraction precipitates. The precipitates were suspended in 2 ml of an assay buffer (50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.1% BSA (bovine serum albumin), 10 mM $MgCl_2$, 100 mM NaCl, 1 μM GDP (guanosine 5'-diphosphate), 0.25 mM PMSF (phenylmethylsulfonyl fluoride), 1 μg/ml pepstatin, 20 μg/ml leupeptin, 10 μg/ml phosphoramidon). The suspension was centrifuged at 100,000 x g for an hour. The cell membrane recovered as precipitates was resuspended in 20 ml of the assay buffer.

After dispensing, the suspension was stored at -80 °C, which may be thawed every time upon use.

The agonist activity of MCH, MCH(2-19), MCH(3-19), MCH(4-19), MCH(5-19), MCH(6-19) and MCH(7-19) was assayed as follows. The rat SLC-1-expression CHO cell membrane fraction was diluted with the assay buffer. After dispensing 173 μl each of the dilution in a polypropylene-made 96-well plate, 2 μl of solutions of MCH, MCH(2-19), MCH(3-19), MCH(4-19), MCH(5-19), MCH(6-19) and MCH(7-19) diluted with DMSO solution in various concentrations and 25 μl of [^{35}S]-guanosine 5'-(γ-thio)triphosphate (manufactured by Daiichi Kagaku Yakuhin K.K.) were charged in each well at the same time (the final concentration of cell membrane: 20 μg/ml, the final concentration of [^{35}S]-guanosine 5'-(γ-thio)triphosphate: 0.33 nM). The reaction solution was reacted at 25 °C for an hour while stirring. The mixture was then subjected to suction filtration through a glass filter (GF-C). The filtrate was further washed 3 times with 300 μl of washing liquid (50 mM Tris-HCl buffer, pH 7.5). After adding 50 μl of a liquid scintillator to the glass filter, the residual radioactivity was measured using a liquid scintillation counter.

The agonist activity of MCH(6-19) and MCH(7-19) decreased by approximately 10 times and 200 times, respectively, as compared to that of MCH, whereas MCH(2-19), MCH(3-19), MCH(4-19) and MCH(5-19) showed almost the same agonist activity as shown in FIG. 7.

Fig. 7



The results of Example 21 can be represented by EC_{50} values as follows.

	EC_{50} (nM)
MCH	1.0
MCH(2-19)	1.2
MCH(3-19)	1.2
MCH(4-19)	1.5
MCH(5-19)	1.7
MCH(6-19)	11
MCH(7-19)	160

Therefore, even considering the agonist activities of underivatized

MCH(2-19), MCH(3-19), MCH(4-19) and MCH(5-19), it was unexpected that BH-MCH(4-19) has remarkably high agonist activities as compared with BH-MCH, BH-MCH(2-19), BH-MCH(3-19) and MCH(5-19).

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 28 day of July, 2004.

Masaaki Mori

Masaaki MORI, PhD